REMARKS/ARGUMENTS:

Applicants have canceled claims 13-40 without prejudice or disclaimer. Applicants reserve the right to reintroduce the subject matter of those claims at a later point in prosecution. Applicants added new claims 41-50. Claims 41-50 are now pending in this application. Reconsideration and allowance of the application is respectfully requested.

Double Patenting

The Office maintained its rejection of claims 13-15, 19-24, 26-32, and 34-38 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-4, 6, 7, 9-13, and 17-19 of copending Application No. 10/087,142 ("the '142 application"). Action at page 3. The Office stated that the rejection is maintained for the reasons given in the Office Action mailed December 15, 2004. *Id.*

Applicants traverse the rejection. The December 15, 2004 Office Action itself ultimately refers back to the double patenting reasons provided in the Office Action mailed March 9, 2004. At that time, the '142 application contained method claims directed to the use of a butyrate for the differentiation of primate pluripotent stem cells. Currently, however, the '142 application does not contain any claims directed to the use of a butyrate in the differentiation process (and, in fact, only one claim of the '142 application cited by the Office for this rejection is still even pending!). Thus, any reasoning employed in the earlier Office Actions is no longer applicable and the double patenting rejection should be withdrawn.

Regardless, Applicants note that the double patenting rejection is only provisional and thus request that the rejection be held in abeyance until, and if, the '142 application issues as a patent (if the current rejection is maintained for any reason).

Rejection under 35 U.S.C. §112, first paragraph (enablement)

The Office rejected claims 13-15, 19-24, 26-32 and 34-38 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Action at page 3. The Office stated that the claims are

enabled for methods using a medium containing 5 mM sodium butyrate. *Id.* at page 4. However, the Office argued that the claims are not enabled for "claims which recite culturing the cells in a medium containing any concentration of butyrate" *Id.*

Applicants respectfully traverse the rejection and disagree with the Office's narrow view that the claims should be limited to a single concentration of the hepatocyte lineage differentiation agent. To make out a prima facie case of lack of enablement, the Office must "establish a reasonable basis to question the enablement provided for the claimed invention." MPEP §2164.04. The Office has failed to establish such a reasonable basis for this rejection.

The instant specification provides multiple working examples using the claimed hepatocyte differentiation agents in the differentiation of embryonic stem cells to hepatocyte lineage cells. Although some of those examples used 5 mM concentrations, other examples used 2.5 mM concentrations (see Examples 7, 9, and 11). Trichostatin A was used at 100 nM in Example 2 (see Table 8). The Office has not proffered any evidence or argument demonstrating that undue experimentation would be required of one skilled in the art to determine other effective concentrations of the hepatocyte lineage differentiation agents.

For example, the Office set forth various arguments in the Action regarding the variability of the several hepatocytes differentiation agents exemplified in Table 7. Action at page 5. However, the Office did not explain, or even attempt to explain, why these arguments apply to the issue of finding other effective concentrations of the hepatocyte differentiation agents. Even assuming that this art is unpredictable, the Office must still explain why one skilled in the art would not be able to successfully vary these concentrations.[1]

The Office also referred to its reasons for rejection cited in its December 15, 2004 Office Action ("December 15th Action"). Action at page 4. In that Office Action, the Office cited the Lee et

[1] As an initial note, the Office should take the skill in this art into account in its analysis because that skill is often found to be quite high. This is relevant when considering the simple nature of the task at issue – finding other effective concentrations of an agent.

al. article in support of its contentions. *See* December 15th Action at page 6. The Office, however, has not shown that the Lee paper is actually relevant to the instant methods. First, the Lee paper studies differentiation in mouse cells, not primate cells. The Office has not proffered any evidence that demonstrates or even suggests that such experimentation in the mouse system is predictive for the primate system. Furthermore, the data in the instant application exemplifies histone deacetylase inhibitors that are effective in promoting differentiation, which is inconsistent with the Lee paper's conclusion that "global deacetylation is necessary for in vitro differentiation of ES cells." Lee paper at page 37 (emphasis added). In addition, the Lee paper only used Trichostatin A and only at concentrations (5 and 10 nM) that are 5% - 10% of the Trichostatin A concentration used in the instant application (100 nM).[2] Applicants note that the instant specification teaches that lower levels of Trichostatin A (10-50 nM) were ineffective. Specification at page 40, lines 12-13. Thus, the relevance of the Lee paper, which was performed in the mouse model and which used far different concentrations of one histone deacetylase inhibitor, to the instant claims must be seriously questioned.

Finally, Applicants note that although they traverse the rejection and disagree with the reasoning and evidence of the Office, they have amended the claims to specifically recite particular differentiation agents. This was done solely to facilitate prosecution and does not indicate acquiescence to the Office's rejections. The specific hepatocyte lineage differentiation agents recited are supported in Table 7 and Table 8, which demonstrate that those agents promote hepatocyte lineage differentiation. In addition, Applicants amended the claims to remove reference to particular percentages as those limitations are unnecessary to define the claimed invention, which is directed to the use of particular agents in a hepatocyte lineage differentiation protocol.

Thus, the Office has not established a prima facie case of lack of enablement because it has not provided any relevant evidence or reasoning supporting its contention that one skilled in the art

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[2] Applicants note that the Office erred in its December 15, 2004 Office Action, stating that Lee showed a "more modest effect on ES cell differentiation" at 5 mM TSA. The experiment that the Office referred to used 5 nM, not 5 mM TSA. *See* Lee paper at page 34.

would not be able to determine other effective concentrations of the claimed hepatocyte lineage differentiation agents without undue experimentation. Applicants request reconsideration and withdrawal of this enablement rejection.

Fees Due

Should the Patent Office determine that a further extension of time or any other relief is required for further consideration of this application, Applicants hereby petition for such relief, and authorize the Commissioner to charge the cost of such petitions and other fees due in connection with the filing of these papers to Deposit Account No. 07-1139, referencing the docket number indicated above.

Respectfully submitted,

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